

Sub C1
Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, and His at position 236.

29. The polypeptide according to claim 28 that comprises SCR 1, 2, 3 and 4 of LHR-A or SCR 1, 2 and 3 of LHR-A as the only structurally and functionally intact SCR domains of CR1.

30. The polypeptide according to claim 28, wherein the polypeptide further comprises interdomain sequences of CR1, wherein at least one of the native amino acids are substituted, wherein the substitutions are selected from the group consisting of Lys at position 59 and Ile at position 124.

31. The polypeptide according to claim 28, wherein the polypeptide has formula (I):

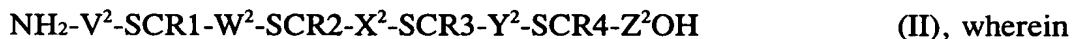


SCR1 comprises residues 2-58 of mature CR1, SCR2 comprises residues 63-120 of mature CR1, SCR3 comprises residues 125-191 of mature CR1, and V¹, W¹, X¹ and Y¹ represent bonds or short linking sequences of amino acids, and wherein there is at least one substitution present in on of the SCRs.

32. The polypeptide according to claim 31, wherein V¹, W¹, X¹ and Y¹ polypeptide comprises interdomain sequences of CR1, wherein at least one of the native amino acids are substituted, wherein the substitutions are selected from the group consisting of Lys at position 59 and Ile at position 124.

33. A polypeptide according to claim 31 wherein W^1 , X^1 and Y^1 comprise residues 59-62, 121-124 and 192-196 of mature CR1, and V^1 represents residue 1 of mature CR1.

34. A polypeptide according to claim 28, wherein the polypeptide has formula (II):



SCR1 comprises residues 2-58 of mature CR1, SCR2 comprises residues 63-120 of mature CR1, SCR3 comprises residues 125-191 of mature CR1, and SCR4 comprises residues 197-252 of mature CR1, and V^2 , W^2 , X^2 , Y^2 and Z^2 represent bonds or short linking sequences of amino acids.

35. The polypeptide according to claim 34, wherein V^2 , W^2 , X^2 and Y^2 polypeptide comprises interdomain sequences of CR1, wherein at least one of the native amino acids are substituted, wherein the substitutions are selected from the group consisting of Lys at position 59 and Ile at position 124.

36. The polypeptide according to claim 34 wherein W^2 , X^2 , Y^2 and Z^2 represent residues 59-62, 121-124, 192-196, and residues 253 of mature CR1, and V^2 represents residue 1 of mature CR1.

37. The polypeptide according to claim 28, wherein the polypeptide has formula (III):

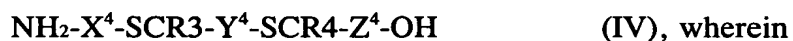


SCR3 comprises residues 125-191 of mature CR1, wherein at least one of the native amino acids are substituted, wherein the substitutions are selected from the group consisting of Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position

161, Lys at position 177, and X³ and Y³ represent bonds or short linking sequences of amino acids.

38. The polypeptide according to claim 37 wherein X³ represents amino acids 122-124 of mature CR1 and Y⁴ represents amino acids 192-196 of mature CR1.

39. The polypeptide according to claim 28, wherein the polypeptide has formula (IV):



SCR3 comprises residues 125-191 of mature CR1, and SCR4 comprises residues 197-252 of mature CR1, wherein at least one of the native amino acids are substituted, wherein the substitutions are selected from the group consisting of Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, His at position 236, and X⁴, Y⁴ and Z⁴ represent bonds or short linking sequences of amino acids.

40. The polypeptide according to claim 39 wherein X⁴ comprises amino acids 122-124 of mature CR1, Y⁴ comprises amino acids 192-196 and Z⁴ comprises amino acid 253 of mature CR1.

41. The polypeptide according to claim 39, wherein X⁴ comprises interdomain sequences of CR1, wherein at least one of the native amino acids are substituted, and wherein the substitution is Ile at position 124.

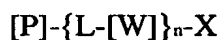
42. A soluble derivative of a soluble polypeptide that comprises in sequence one to four short consensus repeats (SCR) selected from SCR 1, 2, 3 and 4 of long homologous repeat A (LHR-A) as the only structurally and functionally intact SCR domains of CR1 and including at least SCR3, wherein at least one of the native amino acids are substituted,

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wherein the substitutions are selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, His at position 236,

wherein the derivative comprises at least two heterologous membrane binding elements with low membrane affinity covalently associated with the polypeptide, wherein the elements are capable of interacting independently and with thermodynamic additivity with components of cellular membranes exposed to extracellular fluids.

43. The derivative according to claim 42, comprising two to eight membrane binding elements selected from the group consisting of fatty acid derivatives, ligands of integral membrane proteins, sequences derived from the complementarity-determining region of monoclonal antibodies raised against epitopes of membrane proteins, and membrane binding sequences identified through screening of random chemical libraries.

44. The derivative according to claim 42 having the following structure:



in which:

P is the soluble polypeptide,

each L is independently a flexible linker group,

each W is independently a peptide membrane binding element,

n is an integer of 1 or more, and

X is a peptidic or non-peptidic membrane-binding entity which may be covalently linked to any W.

45. A polypeptide derivative having a sequence selected from the group consisting of which is SEQ ID NO. 34, SEQ ID NO. 49 and SEQ ID NO. 51.

46. A DNA polymer selected from SEQ ID NOS consisting of: 1, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, and 30.

47. The DNA polymer of claim 46, wherein the polymer is in a replicable expression vector.

48. The DNA polymer of claim 47, wherein the replicable expression vector is in a transformed host cell.

49. A process for preparing a soluble derivative of a soluble polypeptide that comprises in sequence one to four short consensus repeats (SCR) selected from SCR 1, 2, 3 and 4 of long homologous repeat A (LHR-A) as the only structurally and functionally intact SCR domains of CR1 and including at least SCR3, wherein at least one of the native amino acids are substituted, wherein the substitutions are selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, His at position 236, comprising

expressing DNA encoding the polypeptide portion of said derivative in a recombinant host cell and recovering the product and thereafter post translationally modifying the polypeptide to chemically introduce membrane binding elements.

50. A pharmaceutical composition comprising (A) a therapeutically effective amount of a soluble polypeptide comprising in sequence one to four short consensus repeats (SCR) selected from SCR 1, 2, 3 and 4 of long homologous repeat A (LHR-A) as the only structurally and functionally intact SCR domains of CR1 and including at least SCR3, wherein at least one of the native amino acids are substituted, wherein the substitutions are

selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, His at position 236, and (B) a pharmaceutically acceptable carrier or excipient.

51. A method of treating a disease or disorder associated with inflammation or inappropriate complement activation comprising administering to a subject a pharmaceutical composition comprising (A) a therapeutically effective amount of a soluble polypeptide comprising in sequence one to four short consensus repeats (SCR) selected from SCR 1, 2, 3 and 4 of long homologous repeat A (LHR-A) as the only structurally and functionally intact SCR domains of CR1 and including at least SCR3, wherein at least one of the native amino acids are substituted, wherein the substitutions are selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, His at position 236, and (B) a pharmaceutically acceptable carrier or excipient.